Abnormal Captopril Renogram with a Technetium-99m-Labeled Hippuran Analog


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A case of renovascular hypertension is presented in which the $^{131}$Ihippuran renogram was initially normal, but became strikingly abnormal upon administration of the angiotensin converting enzyme (ACE) inhibitor captopril. The patient presented with fibromuscular dysplasia of the renal arteries, which was shown by hippuran renography to be functionally significant on the right side. She became normotensive after angioplasty of the right renal artery. Hypertension recurred a year later, at which time the renogram was normal without captopril, but showed functionally significant left renal artery stenosis with captopril challenge. Both the conventional agent, $^{131}$Ihippuran, and an experimental new 99mTc-labeled hippuran analog, $^{99m}$TcMAG$_3$, were used. Angiography confirmed progression of disease on the left side, which was successfully treated by angioplasty. Functionally significant unilateral renal artery stenosis was thus demonstrated first on the right side and then, 1 yr later, on the left side, using hippuran and $^{99m}$TcMAG$_3$. Anatomic progression of disease was documented by angiography.


It has been known for many years that renovascular hypertension can be detected by radionuclide renography (1). The test was widely used at one time in this country and even more extensively in Europe. Dissatisfaction with the sensitivity and specificity of the test, in conjunction with improved antihypertensive medications, led to its demise.

Two new events are leading to a renaissance of interest in renography for hypertension. One is the advent of transluminal angioplasty, which is again tilting the balance away from pharmacotherapy, and the other is the use of angiotensin converting enzyme (ACE) inhibitors such as captopril as an adjunct to renography to enhance its sensitivity and specificity. While arteriography can identify stenosis, it furnishes little direct evidence of functional significance. The renogram readily detects impaired function, but may not reveal the cause, so that it complements the arteriogram.

ACE inhibitors cause glomerular filtration rate (GFR) to fall in a kidney with functionally significant renal artery stenosis (FSRAS) (2,3). This was discovered when these agents were found to induce renal failure in patients with solitary kidneys and FSRAS, where compensation by the other kidney was not possible. The phenomenon can be used to enhance the sensitivity of renography, by enhancing the difference between normal and abnormal kidneys (2,3). However, there is no agreement on the details of the technique. An international study, coordinated by Dr. Enza Fommei in Pisa, is in progress to determine the sensitivity and specificity of the captopril renogram when used with either a filtered agent technetium-99m diethylenetriaminepentaacetic acid ($^{99mTc}$DPTA) or a secreted agent iodine-131 hippuran ($^{131}$Ihippuran). We show here a particularly dramatic case revealed only after captopril, which was studied not only with $^{131}$Ihippuran but also with an experimental new hippuran analog, $^{99m}$Tc-mercaptoacetyltriglycine (MAG$_3$) (An investigational new drug in a kit formulation from Mallinckrodt, Inc.) (4–6), administered simultaneously and imaged by a dual channel technique.

CASE REPORT

A 33-yr-old white female was found to be hypertensive on a routine gynecologic examination. Renal angiography at an outside hospital was said to be consistent with fibromuscular disease of the right renal artery. The patient was referred to our institution for consideration of percutaneous transluminal angioplasty (PTA).
Renal scintigraphy was performed using \[^{311}\text{I}]\text{hippuran}, with effective renal plasma flow (ERPF) determined from a single timed blood sample (7). The images showed marked right renal parenchymal retention (Fig. 1). The right kidney accounted for only 12% of the total effective renal plasma flow of 280.6 ml/min (Table 1). Peak times were 23 min for the right kidney and 4 min for the left kidney. Arteriography confirmed significant right renal artery stenosis and a mild left renal artery stenosis, both consistent with fibromuscular dysplasia (Fig. 2). Preangioplasty right and left renal vein renins were 159.3 and 94.4 ng/ml/hr, respectively, consistent with right renal lateralization, with a right to left renal vein renin ratio of 1.7 (A ratio over 1.5 is considered significantly asymmetric.) Percutaneous transluminal angioplasty (PTA) of the right renal artery was performed. Postangioplasty right

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<td>—</td>
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<td>9/17/87 captopril</td>
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\(^{\text{a}}\) Effective renal plasma flow measured from single blood sample (7).

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**FIGURE 1**
Hippuran renograms before (top) and after (bottom) the first (right renal artery) angioplasty. Curves are shown for right kidney (R), left kidney (L) and background (B). Note the impaired blood flow and marked parenchymal retention on the right prior to angioplasty.
and left renal vein renins were 25.0 and 16.7 ng/ml/hr, respectively. The patient became normotensive and was discharged without antihypertensive therapy. A follow-up clinic visit revealed blood pressure of 130/80. Renal scintigraphy performed 3 wk postangioplasty no longer showed parenchymal retention (Fig. 1). The right renal blood flow had improved but was still below normal (Table 1).

One year later, the patient was found to have recurrent hypertension with a blood pressure of 164/106. Renal scintigraphy demonstrated normal images, essentially unchanged from the post-PTA renogram 1 year earlier (Fig. 3). However, quantitation suggested a slight decrease in left renal function (Table 1). The study was repeated with 25 mg of captopril orally one hour before the study, which induced a fall in blood pressure from 140/82 to 102/68. Iodine-131 OIH (0.3 mCi) and [99mTc]MAG3 (5 mCi) were administered simultaneously with dual channel imaging (Figs. 3 and 4). Both imaging agents showed striking parenchymal retention on the left side only, the previously normal side. The right kidney accounted for 42% of the total estimated renal plasma flow with right and left peak times of 3 and 20 min, respectively. The patient again underwent renal arteriography with angioplasty which demonstrated a crudely patent right renal artery and marked progression of the left renal artery stenosis (Fig. 5). Selective left and right renal vein renins prior to PTA were 72.2 ng/ml/hr and 36.2 ng/ml/hr, respectively (ratio 2.0), consistent with functionally significant left renal artery stenosis. A left renal angioplasty was done. The patient again became normotensive and was discharged from the hospital without antihypertensive therapy. Two months later, renal scintigraphy without captopril (Fig. 6) demonstrated essentially normal renal function bilaterally. The study was repeated with 25 mg of captopril given 1 hr prior to imaging. At this time, there was no significant blood pressure response to captopril (118/78 before, 114/74 after). The peak time was delayed on the right, but the images showed pelvic rather than parenchymal retention (Fig. 6). At present, the patient remains normotensive with no medications.

**FIGURE 2**
Right renal arteriograms before (A) and after (B) angioplasty (7/29/86). There is a tight right renal artery stenosis (arrow) in the mid-portion of the main right renal artery that has been relieved by angioplasty (arrow).
When renal artery stenosis is functionally significant, there is increased reabsorption of salt and water with consequent reduction in urine flow and delayed clearance of radiotracer from the affected kidney. With more severe stenosis, in addition to the delay in clearance, there is impaired uptake (7). Captopril exaggerates the delayed clearance by interfering with the angiotensin-mediated autoregulation of GFR. The fall in GFR further reduces urine flow in the affected kidney so that the delay in washout becomes more apparent (2).

On this patient's initial study, the blood flow to the affected kidney was impaired. This was demonstrated both on the images (poor uptake on the right in the first frame of Fig. 1) and from the quantitative measurements (Table 1). Parenchymal transit was prolonged with the retained activity clearly parenchymal rather than pelvic in distribution, a pattern characteristic of FSRAS (3). The parenchymal retention pattern is not seen well with agents such as $[^{99m}Tc]$DTPA that are not actively secreted, because there is no way for their activity to become concentrated in the slowly flowing urine stream. However, it is readily identified on hippuran studies in circumstances when filtration fraction is impaired, such as FSRAS, acute tubular necrosis, or acute transplant rejection. The initial image (0–3 min) is always parenchymal and serves as a useful comparison whenever there is difficulty deciding whether retention is parenchymal or pelvic. Patients with retention...
are thus divided into those with parenchymal retention, which indicates impaired filtration fraction, and those with pelvic retention, which signifies dehydration, obstruction, or pelvic dilatation. In this patient, the pattern of parenchymal retention disappeared after angioplasty though the renal blood flow remained below normal. The postangioplasty study was done after only three weeks, at which time recovery of function may have been incomplete. There may have also been irreversible parenchymal damage.

Progression of disease is not an unusual occurrence in fibromuscular dysplasia. (8). In this case, when hypertension recurred and the renogram was repeated, the fall in total ERPF (though of marginal significance) suggested that the improvement in symmetry was achieved by a fall in left kidney function rather than continued improvement in the right kidney. However, captopril administration was required to confirm this by revealing the characteristic pattern of parenchymal retention on the left side. The pattern was displayed even better with the experimental hippuran analog, [99mTc]MAG3. The better image quality was due to a higher count rate (by a factor of 20) and in spite of using a high-energy collimator. On the final study, after the second successful angioplasty, note that the delayed washout on the right side postcaptopril was due to pelvic rather than parenchymal retention, and thus attributable to suboptimal hydration rather than to FSRAS.

This case is instructive on several counts. The sequence of renograms, arteriograms, and blood pressure responses in this woman with fibromuscular dysplasia leaves little doubt about the diagnosis or course of the disease. On initial presentation, the stenosis was severe enough to give an abnormal renogram even without captopril. When it recurred on the contralateral side, the test was positive only when captopril was used. The images clearly display the distinction between parenchymal and pelvic retention, a diagnostically useful

FIGURE 4
Simultaneous hippuran and [99mTc]MAG3 renograms with captopril prior to second angioplasty. Note similarity between hippuran (top) and [99mTc]-MAG3 (Bottom) images and curves. Despite using a high-energy collimator, the technetium images are of better quality.
A: Left renal arteriogram (7/29/86) at the time of right renal angioplasty: A mild stenosis (arrow) is present in the distal portion of the left renal artery.

B: Left renal arteriogram approximately one year later (7/7/87). There has been marked progress of the stenosis (arrow).

C: Left renal arteriogram immediately after left renal transluminal angioplasty (7/7/87). The stenosis has been successfully dilated (arrow).
feature. The new analog of hippuran, $[^{99m}Tc]MAG_3$, gave results identical to hippuran but with images of improved quality.

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REFERENCES


FIGURE 6
Hippuran renograms with (bottom) and without (top) captopril following the second (left-sided) angioplasty. Note that the retained activity on the right is in the collecting system and not in the cortex, in contrast to the finding with functionally significant renal artery stenosis.